Appendix B

ORIGINAL ARTICLE

A Randomized Trial of Inhaled Cyclosporine in Lung-Transplant Recipients

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ABSTRACT

BACKGROUND

Conventional regimens of immunosuppressive drugs often do not prevent chronic rejection after lung transplantation. Topical delivery of cyclosporine in addition to conventional systemic immunosuppression might help prevent acute and chronic rejection events.

METHODS

We conducted a single-center, randomized, double-blind, placebo-controlled trial of inhaled cyclosporine initiated within six weeks after transplantation and given in addition to systemic immunosuppression. A total of 58 patients were randomly assigned to inhale either 300 mg of aerosol cyclosporine (28 patients) or aerosol placebo (30 patients) three days a week for the first two years after transplantation. The primary end point was the rate of histologic acute rejection.

RESULTS

The rates of acute rejection of grade 2 or higher were similar in the cyclosporine and placebo groups: 0.44 episode (95 percent confidence interval, 0.31 to 0.62) vs. 0.46 episode (95 percent confidence interval, 0.33 to 0.64) per patient per year, respectively ($P=0.87$ by Poisson regression). Survival was improved with aerosolized cyclosporine, with 3 deaths among patients receiving cyclosporine and 14 deaths among patients receiving placebo (relative risk of death, 0.20; 95 percent confidence interval, 0.06 to 0.70; $P=0.01$). Chronic rejection–free survival also improved with cyclosporine, as determined by spirometric analysis (10 events in the cyclosporine group and 20 events in the placebo group; relative risk of chronic rejection, 0.38; 95 percent confidence interval, 0.18 to 0.82; $P=0.01$) and histologic analysis (6 vs. 19 events, respectively; relative risk, 0.27; 95 percent confidence interval, 0.11 to 0.67; $P=0.005$). The risks of nephrotoxic effects and opportunistic infection were similar for patients in the cyclosporine group and the placebo group.

CONCLUSIONS

Inhaled cyclosporine did not improve the rate of acute rejection, but it did improve survival and extend periods of chronic rejection–free survival. (ClinicalTrials.gov number, NCT00268515.)

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Outcomes after lung transplantation are poor as compared with those after heart, kidney, or liver transplantation, with a three-year survival rate of only 55 percent for recipients of lung transplants. Death is commonly due to chronic rejection,[1] which presents histologically as bronchiolitis obliterans[2-7]; the latter is thought to be a complex response to immunologic, ischemic, and infectious injury.[8-11] Preventive and therapeutic strategies for this process have been largely unsuccessful.[12-14]

Since the immunosuppressive effect of cyclosporine is dose-dependent, targeted delivery of this drug might improve efficacy by increasing the concentration of cyclosporine in the allograft. In animal models of lung transplantation, inhaled cyclosporine remains in high concentrations in lung tissue and reduces rejection without toxicity.[15-18] Moreover, in human lung-transplant recipients with refractory acute and chronic rejection, open-label rescue treatment with inhaled cyclosporine improves clinical markers of rejection and improves survival.[19-25] In light of these findings, we tested whether prophylactic inhaled cyclosporine would improve outcomes after lung transplantation.

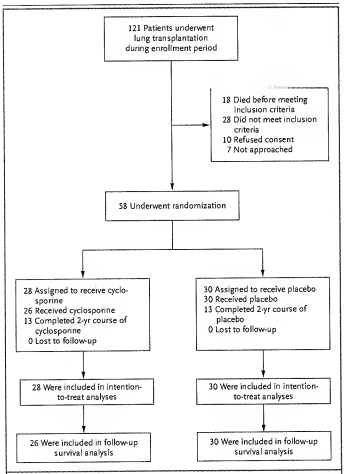

Figure 1. Study Enrollment and Inclusion in the Intention-to-Treat and Survival Analyses.

METHODS

STUDY DESIGN

A randomized, double-blind, placebo-controlled trial of aerosol cyclosporine inhalation, given in addition to conventional immunosuppression, was conducted at the University of Pittsburgh Medical Center with approval of the institutional review board. Recipients of single or bilateral lung transplants who were at least 18 years of age were eligible. Patients were excluded from the study if they had active fungal or bacterial pneumonia, unresolved diffuse alveolar damage, or untreated bronchial stenosis or if they were receiving mechanical ventilation. From November 1998 to August 2001, patients were offered enrollment if they met the study criteria before day 42 after transplantation and were randomly assigned to a treatment group immediately after the provision of written informed consent. Study treatment began as soon as was practically possible thereafter, but no more than 55 days later.

Because mismatches between donor and recipient with respect to cytomegalovirus (CMV) serologic status are known to have an adverse effect on the outcome of transplantation, the randomization was stratified according to donor–recipient CMV status. The two categories were a primary mismatch (a CMV-positive donor and a CMV-negative recipient) and all other serologic combinations. Patients were then randomly assigned to groups according to permuted blocks of four in a 1:1 ratio to receive either inhaled cyclosporine or placebo for two years. All patients were followed for clinical outcome until the last subject completed the scheduled two-year regimen (August 2003). As a result, follow-up ranged from 24 to 56 months.

Novartis Pharmaceuticals provided cyclosporine powder, which was compounded by the Uni-

versity of Pittsburgh experimental pharmacy. University investigators were solely responsible for the trial design, data accrual, and study management. After completion of the study, Chiron obtained a license agreement for inhaled cyclosporine. The analyses presented in this article are those of the university investigators, unless otherwise noted. The data and safety monitoring board took no action regarding early trial cessation.

ADMINISTRATION OF INHALED CYCLOSPORINE

Patients inhaled cyclosporine mixed in propylene glycol (62.5 mg per milliliter) or placebo (propylene glycol alone) initially for 10 consecutive days, then three times weekly with the use of a jet nebulizer (AeroTech II, CIS-US). Patients were instructed to continue treatment for two years. Patients were premedicated by inhalation of 2 percent lidocaine (3 ml) and 2.5 mg of albuterol by means of a nebulizer (Airlife, Cardinal Health). Inhaled cyclosporine was initiated at a dose of 100 mg and increased by incremental doses of 100 mg up to 300 mg or a maximally tolerated dose or an aerosol equivalent volume of placebo. Aerosols were self-administered by the patients and were temporarily discontinued if the treating physician reported an infection that persisted after antibiotic therapy. A study coordinator contacted the patients at least monthly to verify compliance.

TRANSPLANT MONITORING

Patients followed a typical care regimen for patients after lung transplantation, including surveil-

Table 1. **Characteristics of the Patients.***

Characteristic	Cyclosporine (N=28)	Placebo (N=30)	P Value
Age — yr	51.3±2.3	51.7±2.0	0.89
Sex — no. (%)			0.96
Male	17 (61)	18 (60)	
Female	11 (39)	12 (40)	
Diagnosis before transplantation — no. (%)			0.18
Emphysema	10 (36)	19 (63)	
Cystic fibrosis	5 (18)	4 (13)	
Idiopathic pulmonary fibrosis or mixed connective-tissue disease	7 (25)	3 (10)	
Other condition	6 (21)	4 (13)	
Type of transplantation — no. (%)			0.11
Single lung	17 (61)	24 (80)	
Double lung	11 (39)	6 (20)	
Donor–recipient CMV status — no. (%)			0.89
+/+	9 (32)	8 (27)	
+/−	5 (18)	7 (23)	
−/+	7 (25)	9 (30)	
−/−	7 (25)	6 (20)	
No. of HLA mismatches			
HLA-A	1.43±0.12	1.33±0.12	0.58
HLA-B	1.64±0.09	1.80±0.07	0.19
HLA-DR	1.39±0.11	1.33±0.13	0.73
Ischemic time — min	254±15	245±18	0.69
Age of donor — yr	36.0±2.3	35.8±2.8	0.96

* Plus–minus values are means ±SE. Percentages may not sum to 100 because of rounding. CMV denotes cytomegalovirus.

lance bronchoscopy with transbronchial biopsy and bronchoalveolar lavage, spirometry, blood work, and a complete history and physical examination one month after transplantation and at intervals of approximately three months for the first two postoperative years, then at intervals of four to six months. Histologic rejection was defined according to established criteria.[26] Spirometry was performed according to American Thoracic Society standards[27] and the results expressed in terms of the percentage of predicted values.[28] Because bronchiolitis obliterans is not uniformly detectable by biopsy, spirometry is routinely used as a surrogate marker to diagnose chronic rejection. Airflow measurements were evaluated for criteria of the bronchiolitis obliterans syndrome, which was defined as a sustained decrease in the forced expiratory volume in one second (FEV_1) of at least 20 percent from the patient's maximum values in the absence of other causes.[29] Cytomegalovirus status was assessed by CMV pp65 antigenemia at weekly intervals for six months after transplantation.

CLINICAL MANAGEMENT

Both groups received conventional immunosuppression, including tacrolimus (0.06 mg per kilogram of body weight per day), azathioprine (2 mg per kilogram per day), and prednisone (20 mg per day). Subsequent adjustments were made at the discretion of the treating clinician on the basis of lung function and biopsy results. Enhanced immune suppression for treatment of acute rejection (grade 2 or higher), active bronchiolitis obliterans, or both consisted of pulsed corticosteroids (intravenous methylprednisolone at a dose of 1 g per day for 3 days or oral prednisone at a dose of 100 mg tapered to 10 mg over 14 days) or rabbit antithymocyte globulin (Thymoglobulin [SangStat] at a dose of 1.5 mg per kilogram per day for 5 to 7 days). Intravenous ganciclovir was

Table 2. **Characteristics of the Patients after Enrollment.***

Characteristic	Cyclosporine (N = 28)	Placebo (N = 30)	P Value
Days from transplantation to start of treatment	26.2±3.2	23.6±2.5	0.52
Total days of aerosol administration	400±57	431±50	0.70
Percentage of eligible doses received†	57.4±7.8	65.5±6.0	0.41
Patients completing two-year study — no. (%)	13 (46)	13 (43)	
Reasons for discontinuation — no. (%)			0.85
Decision of investigator			
Infection	5 (18)	6 (20)	
Renal failure	0 (0)	1 (3)	
Smoking	0 (0)	1 (3)	
Patient entered in rescue study	1 (4)	2 (7)	
Decision of patient			
Symptoms caused by aerosol administration	2 (7)	2 (7)	
Withdrawal from study	7 (25)	5 (17)	
Duration of follow-up — yr			
Mean	3.1±0.2	2.7±0.2	0.16
Median	3.1	2.6	0.29
Interquartile range	2.4–4.1	2.1–3.9	
No. of tests of pulmonary function per patient	20.5±1.6	18.5±2.0	0.43
Time from transplantation to last test of pulmonary function — yr			
Median	2.9	2.4	0.11
Interquartile range	2.1–3.9	2.0–3.5	

used if the level of antigenemia was more than 10 CMV-positive cells per 2×10^5 leukocytes.

END POINTS

The primary end point of the study was the frequency of histologic acute rejection. Secondary end points included chronic rejection–free survival and overall survival. Chronic rejection was identified on the basis of both histologic markers (for bronchiolitis obliterans) and spirometric markers (for the bronchiolitis obliterans syndrome).[20]

Adverse events were defined as infections requiring treatment, hospitalizations, and symptoms as reported by questionnaire. All evaluations of outcomes were performed in a blinded manner.

STATISTICAL ANALYSIS

Power analysis stipulating a 33 percent difference in the frequency of acute rejection suggested the enrollment of 136 patients on the basis of a two-sided test (α=0.05, β=0.15), an assumed acute-rejection rate of 2.8 events per year, and a dropout rate of 15 percent. The study prespecified a three-year enrollment period. During this time, all qualifying lung-transplant recipients were approached for participation. Enrollment was discontinued after three years, after the accrual of only 58 subjects. The failure to achieve enrollment goals was due to an overestimation of the number of transplantations that would be performed during the accrual period (anticipated number, 180; actual number performed, 121). The study was closed two years after the last subject had been enrolled. All outcome variables were followed until either the death of the patient or the end of the study (in August 2003), independent of the continuation or discontinuation of study medication or the conclusion of the scheduled two-year study-treatment period. Patients were analyzed according to the intention to treat, and no patients were

Table 2. (Continued.)

Characteristic	Cyclosporine (N = 28)	Placebo (N = 30)	P Value
No. of biopsies per patient	12.0±0.7	11.1±0.8	0.43
Time from transplantation to last biopsy — yr			
Median	2.2	2.2	0.99
Interquartile range	1.6–3.3	1.6–2.7	
Daily dose of prednisone AUC — mg‡	12.1±0.6	12.2±0.6	0.88
Calcineurin-inhibitor regimen			0.90
Tacrolimus — no. of patients (%)	23 (82)	25 (83)	
Conversion from tacrolimus to cyclosporine — no. of patients (%)	5 (18)	5 (17)	
Tacrolimus level AUC — ng/ml§	12.4±0.4	11.9±0.4	0.20
Cyclosporine level AUC — ng/ml§	190±19	179±16	0.89
Cytostatic regimen — no. of patients (%)			0.26
Azathioprine	11 (39)	16 (53)	
Mycophenolate mofetil	4 (14)	1 (3)	
Conversion from azathioprine to mycophenolate mofetil	13 (46)	13 (43)	
Daily dose of azathioprine AUC — mg‡	69.5±9.2	63.9±10	0.69
Daily dose of mycophenolate mofetil AUC — mg‡	726±194	738±175	0.96
No. of methylprednisolone pulses — 3 g/patient/yr	0.68±0.18	1.06±0.45	0.45
No. of antithymocyte globulin treatments — per patient per yr	0.17±0.06	0.60±0.45	0.37

* Plus–minus values are means ±SE unless otherwise indicated. Percentages may not sum to 100 because of rounding. AUC denotes area under the concentration–time curve.

† Compliance was determined on the basis of the number of doses patients were eligible to receive up to the time of their death or at two years as a percentage of the doses they received.

‡ Mean daily doses of prednisone, azathioprine, and mycophenolate mofetil were calculated from the reported doses at follow-up visits.

§ Mean calcineurin-inhibitor levels were calculated on the basis of values obtained for each patient.

lost to follow-up. Group means were compared with the use of unpaired, two-tailed t-tests or Mann–Whitney tests. All reported P values are two-sided and have not been adjusted for multiple testing.

The frequency of acute rejection was calculated by determining the number of rejection events of grade 2 or higher per year of study time for each subject. Differences between groups were also considered with the use of a Poisson regression model, with covariates including treatment group, CMV mismatch, and the occurrence or nonoccurrence of a rejection episode before the start of the study treatment. The Poisson model was calculated by Chiron.

Log-rank and Cox proportional-hazards analyses were used to compare survival and chronic rejection–free survival. Nonaerosol covariates that were tested in multivariate analyses included CMV-mismatch status, HLA-mismatch status, the age and sex of the recipient, the age and sex of the donor, smoking history of the recipient, diagnosis beforc transplantation, type of transplantation (single or double), and ischemic time. After closure of the study and unblinding, Chiron performed a follow-up analysis of survival as of June 2004. Statistical analyses were performed with Statview software (SAS).

RESULTS

CHARACTERISTICS OF THE PATIENTS

Of the 121 patients who received lung transplants during the enrollment period, 58 were randomly assigned to a study group and 56 received at least one dose of study medication (inhaled cyclosporine, 26; placebo aerosol, 30) (Fig. 1). The baseline characteristics and clinical management in the two groups were similar (Table 1). The CMV-mismatch status, the number of biopsy procedures, the number of spirometric measurements, immunosuppressive-drug regimens, and tacrolimus levels were similar in patients in the two groups (Table 1 and Table 2).

The mean duration of treatment was 400±57 days among patients receiving cyclosporine and 431±50 days among patients receiving placebo. Thirteen of the 28 patients in the cyclosporine group (46 percent) and 13 of the 30 patients in the placebo group (43 percent) completed the two-year inhalation period. Reasons for discontinuation are given in Table 2. Discontinuation that was initiated by patients (i.e., patients tolerated the aerosol administration but withdrew from the study) and concern on the part of investigators regarding infection accounted for most of the discontinuations in the cyclosporine group (43 percent) and the placebo group (37 percent), and there were no significant differences between the groups. Two patients in each group stopped treatment because of symptoms related to aerosol inhalation. Two patients in the placebo group and one in the cyclosporine group with refractory rejection were withdrawn from the study and entered into the separate open-label, "rescue" trial of inhaled cyclosporine. Two additional patients received open-label therapy after study medication was stopped. All data from these five patients after crossover were included in the statistical results in the intention-to-treat analysis.

ACUTE REJECTION

We performed a total of 335 biopsies in patients in the cyclosporine group and 333 biopsies among patients in the placebo group. The mean number of biopsies (5.5 per patient per year) exceeded the minimum protocol requirements. The mean follow-up for acute rejection (mean time from study initiation to the last biopsy) was 2.4±0.2 years for the cyclosporine group and 2.2±0.2 years for the placebo group (P=0.43). The estimated number of acute-rejection episodes of grade 2 or higher per patient per year after the start of study-drug administration was 0.44 (95 percent confidence interval, 0.31 to 0.62) for the cyclosporine group and 0.46 (95 percent confidence interval, 0.33 to 0.64) for the placebo group. In each group, 17 patients had no more than one event per year; 26 patients in the cyclosporine group and 23 patients in the placebo group had no more than two events per year; and 26 patients in each group had no more than three events per year. A Poisson regression model with control for CMV-mismatch status and the occurrence or nonoccurrence of a rejection episode of grade 2 or higher before study-drug administration demonstrated that there was no significant difference between the treatment groups (P=0.87).

CHRONIC REJECTION

Chronic rejection–free survival was improved among patients who were treated with inhaled cyclosporine as determined by spirometric and histologic evaluation. Figure 2A shows the re-

sults of a hazards analysis of survival free of the bronchiolitis obliterans syndrome, with 10 events in the cyclosporine group and 20 events in the placebo group (relative risk, 0.38; 95 percent confidence interval, 0.18 to 0.82; P=0.01). Figure 2B shows the results of a similar analysis of survival free of histologic bronchiolitis obliterans, with 6 events among patients in the cyclosporine group and 19 events among patients in the placebo group (relative risk, 0.27; 95 percent confidence interval, 0.11 to 0.67; P=0.005). None of the four patients in the cyclosporine group in whom histologic bronchiolitis obliterans was diagnosed were receiving study drug at the time of diagnosis.

There was no significant difference in the number of methylprednisolone pulses or treatments with antilymphocyte globulin between the two groups. However, none of the 28 patients in the cyclosporine group were treated with sirolimus after other therapies for chronic rejection failed (as determined by histologic or spirometric analysis), as compared with 7 of 30 patients in the placebo group (P=0.006). Overall, more patients required treatment for histologic bronchiolitis obliterans in the placebo group (8 of 30 patients) than in the cyclosporine group (2 of 28 patients) (P=0.05).

SURVIVAL ANALYSIS

The use of inhaled cyclosporine was associated with a substantial survival advantage (Fig. 3). There were 14 deaths (47 percent) in the placebo group, as compared with 3 deaths (11 percent) in the cyclosporine group (P=0.005 by log-rank analysis). Multivariate survival regression confirmed that the risk of death for patients receiving placebo was higher by a factor of 5 (relative risk of death in the cyclosporine group as compared with the placebo group, 0.20; 95 percent confidence interval, 0.06 to 0.70; P=0.01) and revealed no significant effect for CMV strata, transplant type, or HLA mismatch.

Ten deaths were attributed to rejection, pneumonia, or sepsis (eight in the placebo group and two in the cyclosporine group). Three other patients with a known previous diagnosis of clinically significant rejection or pneumonia died of either pulmonary embolism (two patients in the placebo group) or congestive heart failure (one in the placebo group). Four patients with a known previous diagnosis of rejection (three with bronchiolitis obliterans) or pneumonia died outside our institution (three in the placebo group and one in the cyclosporine group) without postmortem verification of the cause of death.

A follow-up analysis of survival including all 56 patients who received study medication was conducted during the 10 months that followed the end of the study. During that period, an additional

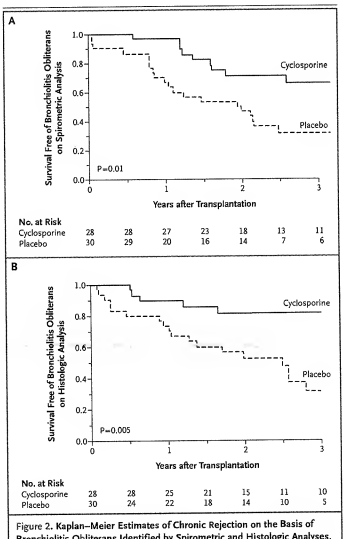

Figure 2. Kaplan–Meier Estimates of Chronic Rejection on the Basis of Bronchiolitis Obliterans Identified by Spirometric and Histologic Analyses.

Multivariate time-to-event regression on the basis of spirometric analysis (Panel A) shows a relative risk of 0.38 for inhaled cyclosporine as compared with placebo (95 percent confidence interval, 0.18 to 0.82; P=0.01 by both Cox proportional-hazards analysis and log-rank analysis). Multivariate time-to-event regression on the basis of histologic analysis (Panel B) shows a relative risk of 0.27 for cyclosporine as compared with placebo (95 percent confidence interval, 0.11 to 0.67; P=0.005 by Cox proportional-hazards analysis and P=0.004 by log-rank analysis).

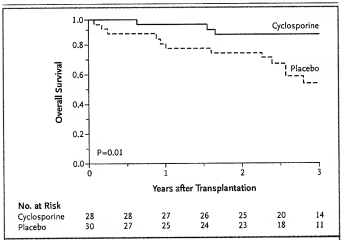

Figure 3. **Kaplan–Meier Estimates of Overall Survival.**
There were 14 deaths in the placebo group (47 percent) as compared with 3 deaths in the cyclosporine group (11 percent). Survival regression yielded a relative hazard of 0.20 for inhalational cyclosporine as compared with controls (95 percent confidence interval, 0.06 to 0.70; P=0.01 by Cox proportional-hazards analysis and P=0.005 by log-rank analysis).

two patients in the cyclosporine group and one patient in the placebo group died. The results of log-rank analysis of survival were similar to those reported at study closure (P=0.02).[30]

INFECTION

The pneumonia rate was not significantly different in the two groups (13 patients in the cyclosporine group and 17 patients in the placebo group, P=0.44), and patients receiving aerosol cyclosporine were no more likely to be treated for infection than were patients in the placebo group (2.3±0.4 vs. 3.1±0.6 courses of antibiotic per patient per year, respectively; P=0.29). The risk of CMV pneumonitis was less in the cyclosporine group (3 of 28 patients) than in the placebo group (10 of 30 patients; P=0.04). The difference was confirmed by Cox proportional-hazards analysis with study drug and donor–recipient CMV status as covariates, with a relative risk of assignment to cyclosporine of 0.27 (P=0.05) and of CMV mismatch of 4.33 (P=0.009) among CMV-positive donors with CMV-negative recipients, as compared with all other combinations.

ADVERSE EVENTS

Both cyclosporine and placebo aerosols were associated with local irritation, including cough, pharyngeal soreness, or dyspnea in 52 percent of study participants on the basis of responses to a questionnaire administered during clinical visits (Table 3). Such symptoms were observed in both groups, were typically transient, and were either mild or moderate in severity. When symptoms occurred, they usually resolved within 30 to 45 minutes after inhalation.

Twelve patients were given a diagnosis of cancer (6 of 28 patients in the cyclosporine group and 6 of 30 patients in the placebo group, P=0.89). Although the overall area under the concentration–time curve (AUC) for the mean serum creatinine level was not significantly different in the two groups (1.5±0.1 mg per deciliter in the cyclosporine group and 1.7±0.1 mg per deciliter in the placebo group), a higher proportion of patients in the placebo group had an AUC mean creatinine level that was more than 1 SD above the all-patient mean (0 of 28 patients in the cyclosporine group and 6 of 30 patients in the placebo group, P=0.01). There was no significant difference between the groups in the number of hospital days per patient per year (23±4 in the cyclosporine group and 48±12 in the placebo group, P=0.07) or the number of hospitalizations per patient per year (2.1± 0.5 in the cyclosporine group and 3.8± 1.0 in the placebo group, P=0.17).

DISCUSSION

Chronic rejection remains the leading cause of death after lung transplantation despite the use of systemic calcineurin inhibitors.[31-33] The immunosuppressive effects of cyclosporine have been shown to be dose-dependent. However, high systemic levels of the drug cannot be achieved without significant toxicity, especially to the kidneys. We hypothesized that the inhalation of an aerosol cyclosporine would provide high pulmonary concentrations of the drug with minimal systemic toxicity, resulting in less acute and chronic rejection. This double-blind, placebo-controlled trial of inhaled cyclosporine given in addition to conventional immunosuppression after lung transplantation was negative with respect to its primary end point, since rates of acute rejection were similar in the group receiving cyclosporine and that receiving placebo. However, survival improved significantly with aerosol cyclosporine, as did the rate of chronic rejection–free survival

(on the basis of both histologic and spirometric analysis).

In the absence of notable differences in rates of acute rejection, a positive result in terms of chronic rejection was unexpected, since previous studies have linked repeated acute rejection events with chronic rejection.[2] Histologically, chronic rejection presents in the airways as bronchiolitis obliterans, whereas acute rejection presents as vasculitis. Bronchioles would have higher local concentrations of a drug as a result of direct aerosol delivery, whereas pharmacokinetic studies suggest a much less substantial vascular concentration of the drug.[34-36] Therefore, it is possible that aerosol cyclosporine has a local airway antiinflammatory effect that decreases the likelihood of chronic rejection while having a lesser effect on vascular acute rejection.

The rates of pneumonia were similar in the two groups, as were serum creatinine levels. More than half the study patients had some level of local irritation (pharyngeal soreness, cough, or dyspnea), with no significant differences noted between patients in the two groups. Less than 10 percent of patients in the cyclosporine group withdrew because of symptoms associated with the aerosol. However, supervision during the first several treatments would probably be required, given the tenuous respiratory status of patients soon after transplantation. Many patients who had some initial minor respiratory symptoms developed a tolerance for the medication after a few treatments.

Local cyclosporine treatment had some benefit in this small, single-center trial. Further experience with inhaled cyclosporine is needed to confirm the magnitude and durability of the observed effects in recipients of single-lung and double-lung transplants.

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A U.S. patent application (20020006901) entitled "Use of Aerosolized Cyclosporine for Prevention and Treatment of Pulmonary Disease" was submitted on February 5, 1999, and assigned to the University of Pittsburgh, with Dr. Iacono listed as inventor. The patent has been licensed by the University of Pittsburgh to Chiron and Novartis Pharmaceuticals. In the event of eventual commercialization of aerosol cyclosporine, a royalty could be paid to the following investigators at the University of Pittsburgh and the State University of New York, Stony Brook: Dr. Iacono, Dr. Dauber, Dr. Smaldone, Dr. Zeevi, and Dr. Burckart. No author reports having any equity interest in either Chiron or Novartis as a stockholder or other related ownership interests. Drs. Iacono, Johnson, and Corcoran report having received consulting fees and Dr. Zeevi lecture fees from Chiron. Dr. McCurry reports having received a grant from Pfizer. Dr. Dauber reports having received lecture fees from and serving on an advisory board for InterMune. No other potential conflict of interest relevant to this article was reported.

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Table 3. **Adverse Events.***

Reported Event	Cyclosporine (N=28)	Placebo (N=30)	P Value
	no. of patients (%)		
Dyspnea	7 (25)	8 (27)	1.00
Wheezing	2 (7)	1 (3)	0.61
Cough	10 (36)	4 (13)	0.07
Headache	3 (11)	1 (3)	0.34
Pharyngeal soreness	12 (43)	12 (40)	1.00
Difficulty swallowing	10 (36)	8 (27)	0.57
Fatigue	0	1 (3)	1.00
Anxiety	2 (7)	0	0.23
Nausea	3 (11)	1 (3)	0.34
Dizziness	2 (7)	1 (3)	0.61
General intolerance	1 (4)	0	0.48
Tremor	1 (4)	2 (7)	1.00
Other condition	1 (4)	4 (13)	0.35

* The number of adverse events was determined on the basis of patients' answers to a questionnaire administered at regularly scheduled clinic visits. Some patients had more than one adverse event. Fisher's exact test was used to compare rates of individual events.

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